REMARKS

This is in response to the Official Action of March 28, 2002. The points raised therein are addressed below in the order originally set forth.

A. The restriction requirement.

The restriction requirement of record now having been made final, the non-elected claims are cancelled herein, without prejudice to the filing of a divisional application thereon.

B. The drawing objections.

Formal drawings are submitted concurrently herewith.

C. The section 112 rejections.

Claims 1-51 and 83-94 stand rejected as indefinite under the second paragraph of 35 USC 112. The concerns raised by the Examiner are addressed below in the order originally set forth.

Claims 1, 5 and 6 are rejected as indefinite in the use of the phrase "capable of". This phrase has been removed from each of these claims by amendment above in favor of a positive recitation, and it is respectfully submitted that this rejection may be withdrawn.

Claim 9 is rejected for lack of antecedent support for "the phospholipid mixture". This phrase has been replaced with "phospholipids" to provide consistency with the claim from which claim 9 depends. It is respectfully submitted that this amendment obviates the need to correct "comprise" to "comprises" in claim 9, and respectfully requested that this rejection now be withdrawn.

Claim 12 has been amended in the manner suggested by the Examiner to render claim 12 definite, and it is respectfully submitted that this rejection may now be withdrawn.

Applicant has also taken this opportunity to amend claim 16 to insert the phrase "or" before the last alternative listed therein, to provide proper grammar within

the claim and to render this claim consistent with the language of corresponding claim 41. No new issues are raised, and entry of this amendment is respectfully requested.

The phrase "and/or" has been removed from claim 17 by rewriting this claim in proper Markush format, and it is respectfully submitted that this rejection may now be withdrawn.

In claims 31 and 32, the phrase "capable of" has been removed to obviate the indefiniteness rejection, and it is respectfully submitted that this rejection may now be withdrawn.

Claim 35 has been corrected to replace "phospholipid mixture" with "phospholipids". It is respectfully submitted that this amendment obviates the need to change "comprise" to "comprises", and respectfully submitted that this rejection may now be withdrawn.

Claim 37 has been amended to recite proper Markush language as suggested by the Examiner, and it is respectfully submitted that this rejection may now be withdrawn.

The phrase "and/or" has been removed from claim 42 by rewriting this claim in proper Markush format, and it is respectfully submitted that this rejection may now be withdrawn.

Claim 83 has been amended to delete the alleged indefinite term "heparin-like molecules", it being understood that this amendment has no bearing on the scope of the generic term "thrombomodulin" in claim 16, from which claim 83 depends.

Claim 88 has been amended to remove the objectionable language "capable of", and to provide antecedent support for the phrase "the initiation phase".

Claim 89 has been amended to remove the phrase "heparin-like molecules", it being understood that this amendment has no bearing on the scope of the generic term "thrombomodulin" in claim 41, from which claim 89 depends.

Claim 94 has been amended to remove the phrase "capable of", consistent with the prior amendments. Claim 94 has also been amended to provide antecedent support for the phrase "the initiation phase".

In view of the foregoing, it is respectfully submitted that the rejections of the claims as indefinite under 35 USC 112, second paragraph, may now be withdrawn.

D. The section 102 rejections.

Claims 1, 3-6, 11, 14-16, and 88 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by **Spillert et al.** (US 6,245,573). Applicants respectfully traverse the rejection based on the following.

Claim 1 has been amended to read as follows:

> Amended Claim 1. A reagent for an assay to determine a hemostatic potential of a blood or plasma sample, said reagent comprising a coagulation activator wherein said coagulation activator is present at a concentration level within a range sufficient to trigger thrombin formation fibrin polymerization but insufficient to result in a complete fibrin polymerization of said blood or plasma sample wherein said reagent may be utilized to assess a hypocoaguable, normal or hypercoaguable condition in a single assay.

A feature of the recited invention is the discovery that when a coagulation activator is present within a specific range, then a single assay may be utilized to determine hypocoagulation, normal or hypercoagulation. This feature permits the assessment of hemostatic potential from a sample because there is a dynamic connectivity between the pathways that lead to thrombin formation resulting in fibrin polymerization (See figure 3 and *Specification, Page 1, lines 20-22)* Unexpectedly, the concentration level of the coagulation activator results in an important advance of the prior art because it enables a single assay for the global measurement of patients. At this concentration the activator is only a trigger. Once there is a threshold concentration of thrombin, further production of thrombin and subsequent fibrin polymerization depends not on the activator concentration but on the interrelationship of the enzymes physiologically responsible for fibrin polymerization: intrinsic tenase complex and the prothrombinase complex as well as the amplification loop.(see figure 3).

The Office Action asserts that Spillert *et al.* teaches a reagent for assessing coagulant activity, i.e. hypocoagulation or hypercoagulation by measuring stasis in the presence of salts. While Spillert, *et al.* teach a reagent for analysis of thrombotic potential (hypercoagulability), they do not describe a reagent for analysis of bleeding tendency (hypocoagulation). As described at Col. 5, lines 45-53, Spillert, *et al.* teach

"that the addition of the metal ions of the present invention to whole blood prior to and/or during the coagulation process alters the coagulation of blood which more closely reflects the thrombotic potential of blood." Spillert et al. teach the addition of certain metal ions to activate the coagulation process. In the prior art, activation of plasma by calcium ions is referred to as the re-calcification time. Further the data do not show the ability to discriminate normal from hypercoagulability.

Additionally, Spillert, *et al.* teach an extrinsic method of analysis where the blood sample is altered with the presence of the metal ions and optional modulator to indicate the development of certain pathological conditions. (See, Abstract). Stated differently, Spillert, *et al.* teach a the use of metal ions to activate the clotting reaction. (See, Col. 3, lines 11-Col. 13, lines 29-36) This is distinguishable from the present invention where the activator is a protein that is added to the sample in an amount that will only trigger thrombin generation. The activator at this concentration is not able to cause substantial fibrin polymerization in the absence of intrinsic tenase. Because the inventive reagent is a trigger it is useful to assess the connectivity and dynamics of the proteins responsible for the hemostatic potential of the entire coagulation system (Specification, Page 14, lines 29-31).

Anticipation under 35 U.S.C. § 102 requires the presence in a single prior art disclosure of each and every element of a claimed invention. *Lewmar Marine Inc. v. Barient Inc.,* 3 USPQ2d 1766, 1767 (Fed. Cir. 1987). Spillert et al. do not teach a reagent to determine hemostatic potential. Further, Spillert et al. do not teach a reagent comprising a coagulation activator that is present at a concentration level within a range sufficient to trigger fibrin polymerization but insufficient to result in a complete fibrin polymerization of said blood or plasma sample, as recited in amended claim 1. Rejected claims 3-6, 11, 14-16, and 88 depend upon amended claim 1, and therefore all rejected claims recite features that are not described in Spillert, *et al.* Applicants respectfully request withdrawal of the rejection.

Claims 1-8, 11-13, 17, 85, and 87-88 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by **Hawkins, *et al.*** (US 5,625,026). Applicants respectfully traverse the rejection based on the following.

The Office Action sets forth that Hawkins, *et al.* provide a teaching of for determining coagulation function (i.e., hypocoagulation or hypercoagulation). While

Hawkins, et al. do provide an advance in the general area of coagulation reagents, the teaching is limited to a teaching of a prothrombin reagent, not a global hemostatic assay. (See, e.g., Abstract) Hawkins, et al. do not teach "coagulation function" to include hypocoagulation and hypercoagulation due to the inherent limitations of a prothrombin reagent.

As a prothrombin time (PT) reagent, by definition the reagent will be used for assessment of bleeding risk (hypocoagulation) and relies on the use of clotting time. The PT assay is based on an addition of a reagent with a very high concentration of a tissue extract such that only the extrinsic pathway is required for fibrin polymerization. The propogation and amplification phases are bypassed using this reagent. The prothombin time is therefore insensitive to many changes in the coagulation pathway and is incapable of detecting hypercoagulability. (See, Specifiation, Page 5, line 22 – Page 6, line 8).

As shown in Figure 3 of the specification, the coagulation process can be divided into four dependent phases, (1) the initiation phase (extrinsic pathway), (2) the propagation phase (intrinsic pathway) (3) the amplification phase, (4) the polymerization phase. All of the phases are effected by regulation and feedback processes referred to as anticoagulant pathways. According to amended claim 1, the presently recited reagent provides a single test that will not bypass any of the phases and therefore has been termed a reagent capable of assessing "global" hemostatic potential. Conversely, Hawkins does not describe a reagent that includes a coagulant activator having a concentration level that would permit a test that assesses both hypercoagulation and hypocoagulation.

Anticipation under 35 U.S.C. § 102 requires the presence in a single prior art disclosure of each and every element of a claimed invention. Hawkins does not teach a reagent that could be used for hypercoagulation, an element recited in amended claim 1. As all rejected claims depend upon amended claim 1, it is respectfully requested that this rejection be removed.

Claims 1-3, 5-10, 14-16, and 85-88 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by **Smirnov, et al.** (US 5,472,852). Applicants respectfully traverse the rejection.

As the Office Action states, Smirnov, *et al.* "disclose a reagent for use in determining the propensity of a patient for thrombotic disease." As is well-recognized by one skilled in the art, thrombotic disease involves hypercoagulation. This is distinct from hypocoagulation. There is no teaching of a reagent that can be used in a hypocoagulation test in Smirnov, *et al.* Amended claim 1 recites, in part, a reagent that may be utilized to assess a hypocoaguable, normal or hypercoaguable condition in a single assay. Thus, it is respectfully submitted that Smirnov, *et al.* fail to anticipate amended claim 1.

More particularly, Smirnov, *et al.* teach a reagent design where one is able to glean only a narrow picture, a quantitative assay where one substrate drives the system. For example, as discussed in the Summary of the Invention (Col. 3, lines 44-46), Smirnov teaches assaying the plasma sample in the presence and absence of exogenous activated Protein C (APC) and the results are compared to those obtained for normal control plasma. Plasmas from patients with lupus anticoagulants are detected by a prolonged clotting time in the absence of exogenous APC. In the presence of APC, these plasmas show a decrease in clotting time. Thus the addition of exogenous APC allows the discrimination of patients with lupus anticoagulants, a hypercoagulable disorder. By adding APC to the assay the test is therefore insensitive to the activation of the Protein C system and is not a global assay of the hemostatic potential of a patient's sample.

In contrast, the presently recited reagent permits a full spectrum assessment of what is happening throughout the coagulation process of a patient sample, not just a narrow picture, like identifying only patient plasma that selectively inhibits APC. A feature of the present invention involves including the coagulation activator in an amount wherein hypercoagulatuion, normal and hypocoagulation are each ascertainable. This is because the coagualtion activator is present only in an amount sufficient to create an environment wherein fibrin polymerization is dependent on the propagation and amplification pathways.. The present invention is sensitive to the Protein C anticoagulant pathway because it relies on activation of endogenous Protein C as a result of the thrombin explosion (see figures 9 & 10). With this discovery, the anticoagulant pathways may each be demonstrated during the coagulation process

rather than driving one specific function of the sample to see if the patient has a propensity of thrombotic disease, as taught by Smirnov, *et al.* (Col. 3, lines 24-25).

Accordingly, it is respectfully requested that this rejection be removed for all claims.

Claims 1-2 4-7, 12-17 and 83-88 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by **Kraus, et al.** (*CA 2252983*). Applicants respectfully traverse the rejection.

As the Office Action states, Kraus, et al. disclose a reagent for use in determining coagulation potential in a sample for diagnosis of thrombotic disease. As is well-recognized by one skilled in the art, thrombotic disease involves hypercoagulation. This is distinctive from hypocoagulation. There is no teaching of a reagent that can be used in a hypocoagulation test in Kraus, *et al.* Amended claim 1 recites, in part, a reagent that may be utilized to assess a hypocoaguable, normal or hypercoaguable condition in a single assay.

As discussed in the Specification at Page 8, line 16 – Page 9, line 15, Kraus, et al. teach a method limited to determining anticoagulant potential. Kraus, *et al.* do not teach global hemostatic potential, as assessed by using the presently recited reagent. By limiting the assay to anticoagulant potential, Kraus, et al. do not provide an assay that would be sensitive to defects in the propagation or amplification phases of the coagulation process shown in Figure 3. Further, Kraus et. al. describe a reagent wherein a modulator of the Protein C system is added in large amounts such that thrombin generation is inhibited and the assay is sensitive to only the anticoagulant potential of the sample and does not measure fibrin polymerization but relies on the measurement of the time of clot initiation. Accordingly, Applicants respectfully request withdrawal of the rejection.

E. The section 103 rejections.

Applicants respectfully traverse all rejections based Section 103 based on the following.

The Office Action utilizes the prior art cited under the Section 102 rejections as the basis of the Section 103 rejections. As discussed above, the prior art teaches reagents utilized for either assessing hypercoagulation or hypocoagulation, not both in

one test. Amended claim 1 recites, in part, a reagent that may be utilized to assess a hypocoaguable, normal, or hypercoaguable condition in a single assay. Similarly, independent claim 27 also recites, in part, a reagent that may be utilized to assess a hypocoaguable, normal, or hypercoaguable condition in a single assay. All rejected claims depend upon amended claim 1 or claim 27.

As discussed in the Specification, assays such as those taught by the cited prior art currently assess variations in one or two phases of the coagulation process. (Specification Page 5, lines 17-21) For clinicians having a need to assess multiple blood samples of patients that may demonstrate hypocogulation or hypercoagulation, multiple screening assays had to be used because the prior art did not teach a single test to assess samples over the spectrum of the coagulation process. The suggestion in the Office Action that one skilled in the art could merely take the teachings of hypocogulation assays and hypercoagulation assays and conduct routine experimentation to obtain a global assay is inconsistent with the teaching of the prior art of record. As discussed in the Specification, prior to the presently recited invention, there was a long felt need to have a global assay yet the state of the art prior to the invention required the multiple assay approach.

Claims 18-20, 25-34, 36-51, 91 and 93-94 stand rejected as obvious under 35 USC 103 over **Spillert,** *et al.* or **Hawkins,** *et al.* This rejection is respectfully traversed.

As discussed in the previous section, Spillert, *et al.* teach a reagent for thrombotic potential, hypercoagulation. There is no teaching of utilizing the same reagent for a hypocoagulatuion test. Further, Spillert, *et al.* do not suggest that the reagent might be altered such that both hypercoagulation and hypocoagulation might both be measured with a single reagent. Indeed, a close reading of Spillert, *et al.* shows that the design of Spillert, *et al.* is for a single reaction versus a full spectrum approach made possible by the concentration level of the coagulation activator of the reagent recited in amended claims 1 and 27. Accordingly, it is respectfully submitted that the rejected claims are patentably distinct over Spillert, *et al.* Applicants respectfully request the withdrawal of this rejection based on Spillert, *et al.*

Hawkins, *et al.* teach a reagent for a prothrombin test (PT reagent), hypocoagulation. There is no suggestion in this reference that would prompt one

skilled in the art to manipulate the PT reagent taught by Hawkins, *et al.* in a manner to extend the reagent for use in a global hemostatic potential assay. As discussed previously, Hawkins, *et al.* are teaching a high concentration of tissue extract that would make the assay incapable of detecting hypercoagulability and is restricted to the use of clotting time. As a PT reagent the invention is incapable of measuring deficiencies in the propagation phase and is not sensitive to the interrelationships of the components responsible for throbin formation. As amended claims 1 and 27 recite, in part, the invention provides a reagent that may be used to determine hypercoagulability, normal or hypocoaguability in a single test. Hawkins, *et al.* does not render obvious the presently claimed invention because there is no motivation to take the PT reagent and make it a "global" reagent nor is there a suggestion on how one skilled in the art might accomplish extending the function of a PT reagent. As all rejected claims depend from amended claim 1, all rejected claims are patentably distinct over Hawkins, *et al.* Removal of this rejection is respectfully requested.

Claims 21-22, 27-29, 31-36, 43-47 and 91-94 stand rejected as obvious over **Smirnov, *et al.*** This rejection is respectfully traversed.

As the Office Action states, Smirnov, *et al.* "disclose a reagent for use in determining the propensity of a patient for thrombotic disease." Thrombotic disease is associated with hypercoagulation. There is no suggestion in Smirnov, *et al.* that their reagent might be utilized for hypocoagulation. Indeed, as discussed in more detail in the Section 102 section above, Smirnov, et al. teach away from a global reagent by teaching a quantitative, specific assay where one substrate drives the system. There is no suggestion that the reagent may have usefulness in a single test for assessing hypercoagulability, normal or hypocoagulability in a single test because the design of the Smirnov, et al. reagent precludes assessing the various coagulation pathways because Smirnov is looking at only a portion of the coagulation process. The rejected claims depend from independent claims 1 and 27, both of which include the feature use of the reagent to assess a hypocoagulable, normal or hypercoaguable condition in a single assay. Accordingly, Applicants respectfully request that this rejection be removed.

Claims 23-24, 27-28, 30-33, 37-42, 46-51[1], 89-91, and 94 stand rejected as obvious under 35 USC 103 over **Kraus, *et al.*** This rejection is respectfully traversed.

As provided by Applicants in the Specification (Page 8, line 16 - Page 9, line 15), Kraus, *et al.* describe a reagent and method limited to determining the anticoagulant potential (hypercoagulation) of a sample by adding thrombomodulin and thromboplastin in a coagulation test. In the method taught by Kraus, et al. the emphasis is on dilutions of thromboplastin such that thrombin is produced at a rate slow enough to enable sufficient activation of protein C during measuring time of the coagulation apparatus. Further the thrombomodulin is added in high concentration such that most of the Protein C is converted to activated Protein C and the assay is directed towards assessing the Protein C potential in the sample. Under these conditions the substrate specificity of thrombin is altered towards Protein C and is not available to act on its substrate, fibrinogen. A disadvantage of this method is that because the assay depends on clot time, the amount of thromboplastin is more restrictive and higher concentrations are required to compensate for increases in clotting time when thrombomodulin is added. Thus, this method teaches away from the global hemostasis assay provided by reagent claimed by Applicants. The Kraus, *et al.* method focus on assessing anticoagulant potential (hypercoagulation) and is insensitive to defects in the propagation and amplification phases, thus making it inappropriate for use as a reagent for a single global test, of hemostasis. Accordingly, it is submitted that the presently rejected claims are patentably distinct from Kraus, *et al.* Removal of this rejection is respectfully requested.

[1] The official action recites "46-47, 46-51." Applicants assume, for the purpose of a complete response, the rejection applies to Claims 46-51, but would be grateful if the Examiner would review these claims and clarify this point.

F. Conclusion.

The changes made by the amendments above are shown in the attached **"Version with Markings to Show Changes Made".**

It is respectfully submitted that this application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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PATENT TRADEMARK OFFICE

Enclosures:
Associate Power of Attorney
Formal Drawings

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner For Patents, Washington, DC 20231, on September 26, 2002.

Vickie Diane Prior
Date of Signature: September 26, 2002

Version with Markings to Show Changes Made

1 (amended). A reagent for an assay to determine a hemostatic potential of a blood or plasma sample, said reagent comprising[:] a coagulation activator [capable of allowing assessment of the hemostatic potential of blood or plasma] wherein said coagulation activator is present at a concentration level within a range sufficient to trigger a thrombin formation but insufficient to result in a complete fibrin polymerization of said blood or plasma sample wherein said reagent may be utilized to assess a hypocoaguable, normal or hypercoaguable condition in a single assay.

5 (amended). The reagent of claim 1, wherein the reagent [is capable of indicating] indicates a sample to be any of hypocoagulable, normal or hypercoagulable, depending upon the condition of the patient from which the sample was taken.

6 (amended). The reagent of claim 1, wherein the reagent [is capable of indicating] indicates a patient, from which the sample was taken, to have any of thrombotic tendency, hemorraghic tendency, or stasis, depending on the patient.

9 (amended). The reagent of claim 8, wherein the [phospholipid mixture] phospholipids comprise all of phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine and at a ratio of approximately from 1 to 10 mole percent phosphatidylserine and from about 5 to 30 mole percent phosphatidylethanolamine and the remainder phosphatidylcholine.

12 (amended). The reagent of claim 4, wherein the metal cation is a divalent metal cation selected from the group consisting of magnesium, calcium or manganese.

16 (amended). The reagent of claim 15, wherein the protein C activator is purified human thrombomodulin, purified non-human mammalian thrombomodulin, soluble or membrane associated thrombomodulin, native thrombomodulin or

thrombomodulin reconstituted with phospholipids, partially or fully glycolsylated thrombomodulin, or fully deglycosylated thrombomodulin.

17 (amended). The reagent of claim 1, further comprising at least one member of the group consisting of buffers [and/or] and stabilizers.

27 (amended). A reagent comprising: a coagulation activator at a concentration of 11 picomolar or less wherein said reagent may be utilized to assess a hypocoaguable, normal or hypercoaguable condition in a single assay.

31 (amended). The reagent of claim 27, wherein the reagent [is capable of indicating] indicates a sample to be any of hypocoagulable, normal or hypercoagulable, depending upon the condition of the patient from which the sample was taken.

32 (amended). The reagent of claim 27, wherein the reagent [is capable of indicating] indicates a patient, from which the sample was taken, to have any of thrombotic tendency, hemorraghic tendency, or stasis, depending on the patient.

35 (amended). The reagent of claim 34, wherein the [phospholipid mixture] phospholipids comprise all of phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine and at a ratio of approximately from 0 to 10 mole percent phosphatidylserine and from about 5 to 30 mole percent phosphatidylethanolamine and the remainder phosphatidylcholine.

37 (amended). The reagent of claim 30, wherein the metal cation is a divalent metal cation selected from the group consisting of magnesium, calcium or manganese.

42 (amended). The reagent of claim 27, further comprising at least one member selected from the group consisting of buffers [and/or] and stabilizers.

83 (amended). The reagent of claim 16, wherein the thrombomodulin comprises heparin [or heparin-like molecules].

88 (amended). The reagent of claim 1, wherein said fibrin polymerization is preceded by an initiation phase, and wherein the coagulation activator [is capable of detecting] detects defects in the initiation phase.

89 (amended). The reagent of claim 41, wherein the thrombomodulin comprises heparin [or heparin-like molecules].

94 (amended). The reagent of claim 27, wherein said coagulation activator is present at a concentration level within a range sufficient to trigger a fibrin polymerization, wherein said fibrin polymerization is preceded by an initiation phase, and wherein the coagulation activator [is capable of detecting] detects defects in the initiation phase.